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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,708	SILENCE, KAREN	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,22 and 34-59* is/are pending in the application.

4a) Of the above claim(s) *39 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,22, 34-38, 40, and 42-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignments*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/22/07, 12/28/07, 1/16/08, 3/18/08, 10/16/08.

DETAILED ACTION

1. Applicant's response received October 16, 2008 is acknowledged.

Claims 3-21 and 23-33 have been canceled.

Claims 1, 2, 22, and 34-59 are pending in the instant application.

Applicant's election without traverse of the antibody species of SEQ ID NO:5 in the reply filed on October 16, 2008 is acknowledged.

Claims 39 and 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 16, 2008.

Claims 1, 2, 22, 34-38, 40, and 42-59 are under examination in this office action as they read on the elected antibody species of SEQ ID NO:5

Information Disclosure Statement

2. The IDS forms received 10/22/07, 12/28/07, 1/16/08, 3/18/08, and 10/16/08 are acknowledged and have been considered.

Specification

3. The title and abstract are objected to because they are not specific for the material that is being claimed in the instant application. Specifically, the title does not mention single domain antibodies that bind von Willebrand Factor, and the abstract discloses antibodies of multiple distinct specificities in addition to vWF. Appropriate amendments to the title and abstract are required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 36-38, 40, 42, and 51-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a large genus of heavy chain antibodies and heavy chain antibody fragments which are at least 70% identical to the entirety of a fragment of SEQ ID NO:5. SEQ ID NO:5 is disclosed as a heavy chain antibody which binds to the A1 domain of von Willebrand Factor (vWF).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene (in the instant case, a peptide) does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes (peptides) may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984)

(affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has also noted that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

Heavy chain antibodies are distinct in that they comprise only a single polypeptide chain, and thus only have 3 CDRs which are responsible for antigen binding. However, the majority of antigen contacts are still found within the CDRs (Ghahroudi et al., of record, see entire document). Note that the instant claim language allows for changes in the amino acid sequence of the claimed antibody to occur anywhere, including within the CDR regions. The instant specification does not appear to define, and the instant claims do not recite, a specific structure that must be maintained such that the property of binding to vWF is maintained. Thus the structure recited in the instant claims (>70% identity) does not appear to be correlated with the

recited function of binding vWF. Therefore, a skilled artisan would reasonably conclude that applicant was not in possession of the full breadth of the claimed genus of heavy chain antibodies and antigen binding fragments thereof at the time the instant invention was filed.

6. Claims 36-38, 40, 42, and 51-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies comprising SEQ ID NO:5 or fragments of SEQ ID NO:5 that maintain binding to the A1 domain of von Willebrand Factor (vWF), does not reasonably provide enablement for antibodies and fragments which comprise 70% identity to SEQ ID NO:5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed a large genus of antibodies and antibody fragments that bind vWF and are structurally similar in that they comprise 70% or more identity to either the entirety or a fragment of SEQ ID NO:5. SEQ ID NO:5 is disclosed as being a heavy chain antibody.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

Heavy chain antibodies are distinct in that they comprise only a single polypeptide chain, and thus only have 3 CDRs which are responsible for antigen

binding. However, the majority of antigen contacts are still found within the CDRs (Ghahroudi et al., of record, see entire document). Note that the instant claim language allows for changes in the amino acid sequence of the claimed antibody to occur within the CDR regions. Since mutating CDR residues in regular antibodies is known in the art to be unpredictable as taught by Rudikoff et al., mutating CDR residues in heavy chain antibodies is also unpredictable, especially given that heavy chain antibodies comprise a smaller number of residues which contact antigen.

Therefore, based upon the guidance of the specification and the teachings of the prior art it does not appear that a skilled artisan could make and use the invention as instantly claimed without conduction additional unpredictable research.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 2, 22, 34-38, 40, 42-46, 51, 52, 54, and 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Frenken et al., US Patent 6,517,829.

Frenken et al. disclose *Camelidae* heavy chain antibodies (VHH) which are greater than 70% identical to SEQ ID NO:5 of the instant specification (see entire document and the enclosed sequence alignment). These antibodies are further disclosed as being present in multiple copies on the surface of cells which are suitable for oral ingestion.

It is noted that Frenken et al. do not disclose that their antibodies are specific for vWF. However, the instant claims, such as claim 36, indicate that 70% or greater

identity to a reference sequence is the amount of structure that must be maintained to retain recited functional attributes. Note that the antibodies disclosed by Frenken et al. comprise more structural identity to SEQ ID NO:5 than what is required by the claims and that the PTO lacks facilities to test reagents for undisclosed functional attributes. Applicant is reminded that where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 2, 22, 34, 35, 43, 44-50, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagano et al. (US Patent 5,916,805, of record) in view of Ghahroudi et al. (FEBS Letters, 1997, 414:521-526, of record).

Nagano et al. disclose antibodies that bind human vWF and pharmaceutical compositions comprising said antibodies (see entire document, particularly claims 1-20 and columns 4, 10, and 11). Such antibodies and compositions are suitable for intravenous administration (see particularly the paragraph spanning columns 10 and 11) and can be used to treat numerous diseases due to their anti-thrombotic activity (see particularly the abstract). It is further disclosed that humanized antibodies are preferred

for use in humans because they exhibit less immunogenicity and have longer half-lives in the bloodstream (see particularly lines 33-44 of column 10). This disclosure differs form the instant claimed invention in that heavy chain antibodies from *Camelidae* animals are not disclosed.

Ghahroudi et al. disclose methods of obtaining camel heavy chain (VHH) antibodies (see entire document, particularly the abstract). They disclose that VHH offer the advantages of being small, easily purified, and have greater stability as compared to conventional antibodies and antibody fragments such as Fab (see particularly the abstract and discussion). It is further disclosed that bi- and mutlivalent molecules made up of VHH are desirable as they will comprise increased avidity for their specific antigen (see particularly the last paragraph of page 525).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make VHH that bind vWF. Motivation to do so comes from the disclosure of Nagano et al. that antibodies which bind vWF are useful as antithrombotics in treating disease and the disclosure of Ghahroudi et al. that VHH are cheaper and more stable than other antibody forms. Thus by making VHH the ordinary artisan would gain the advantages of decreased cost and increased stability as compared to the antibodies of Nagano et al. A person of ordinary skill the art also would be motivated to humanize the VHH because humanization decreases the immunogenicity of the therapeutic antibody as disclosed by Nagano et al and would be motivated to make VHH multimeric to increase their avidity for antigen as disclosed by Ghahroudi et al.

11. Claims 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagano et al. (US Patent 5,916,805, of record) in view of Ghahroudi et al. (FEBS Letters, 1997, 414:521-526, of record) as applied to claims 1, 2, 22, 34, 35, 43, 44-50, and 55 above, and further in view of Griffiths et al., US Patent 5,670,132.

The inventions rendered obvious by the disclosures of Nagano et al. and Ghahroudi et al. have been discussed above and differ from the instant claimed invention in that they do not disclose pegylated antibodies.

Griffiths et al. discloses that pegylating antibodies is advantageous because it reduces immunogenicity and increases circulatory half lives (see entire document, particularly lines 29-45 of column 2).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to pegylate the antibodies rendered obvious by the disclosure of Nagano et al. and Ghahroudi et al. to reduce the immunogenicity and increase half life when said antibodies are used in pharmaceutical compositions for methods of treatment.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 2, 22, 34-38, 40, and 42-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 16, 18, 19, 45, 56, and 66 of copending Application No. 10/534,349. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims recite antibody products and pharmaceutical

compositions which comprise the elected species of SEQ ID NO:5 as evidenced by the enclosed sequence alignment. Note that as part of the response received October 18, 2008, applicant indicated that SEQ ID NO:5 encompassed claims 1, 2, 22, 34-38, 40, and 42-59. As such, even though the copending claims do not recite binding affinities or Kabat numbering, since the copending claims recite a sequence which comprises SEQ ID NO:5 and SEQ ID NO:5 comprises all the properties recited in the instant claims, the products claimed in the copending application necessarily comprise the recited functional and structural properties. Note that the instant claims are broader in scope than the copending claims since the copending claims recite specific sequences whereas the instant claims also recite percent homology and functional fragment language.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 56-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 16, 18, 19, 45, 56, and 66 of copending Application No. 10/534,349 in view of Griffiths et al., US Patent 5,670,132.

The inventions disclosed in the copending application have been discussed above and differ from the instant claimed invention in that the copending claims do not recited that the antibodies are pegylated.

Griffiths et al. discloses that pegylating antibodies is advantageous because it reduces immunogenicity and increases circulatory half lives (see entire document, particularly lines 29-45 of column 2).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to pegylate the antibodies recited in the copending claims to reduce the immunogenicity and increase half life when said antibodies are used in pharmaceutical compositions for methods of treatment.

This is a provisional obviousness-type double patenting rejection.

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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